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Clinical trial

Double blind controlled trial of oral vancomycin as adjunctive treatment in acute exacerbations of idiopathic colitis

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SUMMARY A prospective double blind trial of vancomycin *vs* placebo was undertaken in 40 consecutive adult patients with exacerbation of idiopathic colitis (33 ulcerative colitis, seven Crohn's disease). Vancomycin or placebo (500 mg six hourly) was given for seven days in addition to routine medical therapy. Although there was no significant overall difference in outcome between the two groups, there was a trend towards a reduction in the need for operative intervention in patients with ulcerative colitis treated with vancomycin compared with controls. The efficacy of vancomycin was not attributable to its known action against *C difficile*, which was not isolated from any of the patients. The data suggest that microbiological factors may play a part in the pathogenesis of ulcerative colitis and that further studies using antimicrobials are desirable.

Acute exacerbations of idiopathic colitis (ulcerative colitis and Crohn's disease) in many respects resemble the clinical picture found in acute infective colitis and this suggests that microorganisms may have some aetiological role in the pathogenesis of idiopathic colitis. In spite of this and although the use of tetracycline has been advocated as part of a treatment package,[1] controlled trials of antimicrobials in this condition have been limited to the sulphonamides.[2 3] Vancomycin is a non-absorbable antibiotic active against Gram-positive organisms,[4] attaining a high concentration in faeces when given orally. It has been successfully used in treating pseudomembranous colitis caused by *Staphylococcus aureus* and *C difficile* which are highly sensitive to it *in vitro*.[5 6] While there are sound bacteriological reasons why vancomycin should be of value in disease caused by either of these organisms, there remains a possibility that its efficacy may result from other effects on the faecal flora. An additional justification for a trial of vancomycin in exacerbations of idiopathic colitis is that *C difficile* enterotoxin has been implicated as an aggravating factor in some patients with this disease.[7 8]

This paper describes a double blind controlled trial of oral vancomycin in consecutive patients admitted to hospital in acute exacerbation of idiopathic colitis. The aims of the trial were to determine whether vancomycin was of value as an adjunct to the routine treatment of exacerbations and, if so, whether this benefit could be related to an increased faecal carriage of *C difficile*. The study was approved by the local ethical committee.

Methods

PATIENTS

From March 1979 to December 1981, adult patients admitted to the General Infirmary at Leeds with acute idiopathic colitis were interviewed and their informed consent to enter the trial was obtained. They were questioned and examined by an independent assessor and underwent sigmoidoscopy, barium enema, and rectal biopsy. The patient was entered into the trial provided that typical changes of idiopathic colitis[9] were found in the rectum and extended into the sigmoid colon beyond the limit of the sigmoidoscope, or typical radiological changes were found at barium enema[10] and that the disease

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satisfied the criteria for inclusion into the moderate, or severe categories of Truelove and Witts.[11] Patients were randomised to receive vancomycin or placebo 500 mg six hourly for seven days according to a code held by the central pharmacy and which was not known to the attending physicians. All patients received bed rest and prednisolone 40 mg/day in divided doses; infusions of blood, albumin and electrolytes were given as required to maintain the blood haemoglobin concentration above 12 g/dl and the plasma albumin concentration greater than 36 g/l. Routine haematological and biochemical measurements were made every two days and stool frequency was recorded daily with details of consistency and the presence or absence of blood. The prednisolone dosage was reduced stepwise in all patients by 5 mg decrements every three days provided that all the following conditions applied throughout the previous 72 hour period; three or fewer bowel movements per day, absent to mild pain or malaise, and weight loss less than 1 kg. In patients who failed to fulfil these criteria, the dosage of prednisolone was not reduced.

At the time of admission to hospital, faecal samples were sent to the routine laboratory for bacteriological analysis and conventional bacterial pathogens were sought including *Staphylococcus aureus* and *C difficile*.[12 13] *C difficile* toxin was assayed on Hep-2 cell monolayers (Flow Laboratories Limited, Rickmansworth, UK) using the technique described by George.[14]

The trial end point was reached either when the patient was discharged from hospital or when surgery was carried out. The indications for surgical intervention were: severe continuous or worsening symptoms while on medical therapy and/or the occurrence of life threatening complications. The decision to operate was taken jointly by the physician in charge of the case and an independent surgeon, neither of whom had any knowledge as to whether active or placebo vancomycin had been prescribed.

Results

PATIENT SAMPLE AND DIAGNOSIS

Forty patients were admitted to the trial and their age, sex, diagnosis and duration, and extent of disease are shown in Table 1. Twenty two patients were randomly allocated to receive active vancomycin while 18 received placebo. Eighteen of the vancomycin group had ulcerative colitis and four had Crohn's disease. Among the placebo patients, 15 had ulcerative colitis and three Crohn's disease. The majority of the patients in both groups were in exacerbation of established disease which had failed to settle on outpatient therapy and only five patients (four in the vancomycin group and one in the placebo group) presented within a year of onset of their disease. In the vancomycin group there were 11 men and 11 women with a mean age of 39·1±13·2 years and the mean duration of disease was 6·1±6·5 years. In the control group there were 12 men and six women with a mean age of 35·4±12·4 years and the mean duration of disease was 7·4±4·6 years.

Table 1 *Details of patient groups*

	Vancomycin	*Placebo*
Patients (no)	22	18
Men	11	12
Mean age (±SD) (yr)	39·1±13·2	35·4±12·4
Mean duration of disease (±SD) (yr)	6·1±6·5	7·4±4·6
Ulcerative colitis		
Total	12	8
Subtotal	2	1
Proctosigmoiditis	4	6
Crohn's disease		
Total	2	3
Segmental	2	

EXTENT OF DISEASE

Of the patients in the vancomycin group, 14 patients (12 ulcerative colitis, two Crohn's disease) had total colonic involvement as compared with 11 in the placebo group (eight ulcerative colitis, three Crohn's disease). One of the placebo patients (no 35) had small bowel involvement as well. Two patients with ulcerative colitis in the vancomycin group and one in the placebo group had subtotal-colonic involvement which was defined as disease extending proximal to the splenic flexure, but not involving the hepatic flexure at barium enema examination. Four patients with ulcerative colitis in the vancomycin group and six in the placebo group had proctosigmoiditis only.

OUTCOME OF TRIAL

Overall there was no significant difference in outcome between the patient groups. Table 2 shows that four patients receiving vancomycin and seven receiving placebo came to surgery, the details and indications for which are given in Table 3. All but one of the patients needing urgent operation in each group were treated surgically at an interval of 12–46 days after admission. Though the primary aim of the study was to evaluate the role of oral vancomycin as adjunctive treatment in acute exacerbations of idiopathic colitis irrespective of whether because of ulcerative colitis or Crohn's disease, nevertheless, if

Table 2 *Details of each patient included in the trial and their outcome*

No	*Age*	*Sex*	*Duration*	*Diagnosis*	*Extent*	*Severity*	*Short term outcome*	*Long term outcome*
Vancomycin patients								
1	58	F	4 m	UC	PS	Severe	Settled	1 admission at 1 year, mild attack
2	31	M	5 yr	UC	Total	Severe	Settled	1 mild attack at 18 months
5	36	F	7 yr	UC	PS	Severe	Settled	Surgery at 6 months
7	30	M	6 yr	UC	Total	Moderate	Settled	Surgery at 3 months
8	36	M	5 yr	UC	Total	Severe	Settled	Surgery at 3 months with fulminant attack
9	31	M	1 yr	UC	Total	Moderate	Settled	Remission
11	36	M	2 yr	UC	Subtotal	Moderate	Settled	Remission
13	40	F	6 m	UC	Total	Severe	Settled	1 mild attack at 6 months
17	46	F	6 yr	UC	PS	Moderate	Surgery	—
18	45	M	1 yr	UC	Total	Severe	Settled	1 severe attack at 9 months
19	55	M	4 yr	UC	Total	Moderate	Settled	Remission
20	19	F	4 yr	UC	Total	Moderate	Settled	Remission
22	34	F	3 yr	UC	Total	Moderate	Settled	Remission
25	30	M	12 yr	CC	Patchy	Severe	Settled	Mild continuous symptoms
26	43	M	14 yr	CC	Total	Moderate	Settled	Remission
28	79	F	27 yr	UC	Total	Severe	Settled	1 mild attack at 4 months
30	30	M	3 yr	UC	Total	Severe	Surgery	—
32	37	F	10 yr	UC	Total	Moderate	Settled	Remission
35	28	F	4 yr	CC+SB	Total	Severe	Surgery	—
36	54	M	17 yr	CC+SB	Patchy	Severe	Surgery	—
38	26	F	4 m	UC	Subtotal	Moderate	Settled	1 admission at 3 months
39	35	F	10 m	UC	PS	Moderate	Settled	Remission
Placebo patients								
3	64	M	8 yr	UC	Total	Severe	Surgery	—
4	28	F	3 yr	UC	PS	Severe	Surgery	—
6	39	F	14 yr	UC	Total	Severe	Surgery	—
10	39	M	8 yr	UC	Total	Moderate	Surgery	—
12	33	M	3 yr	CC	Total	Moderate	Settled	Remission
14	18	M	4 yr	UC	PS	Severe	Surgery	—
15	36	M	13 yr	UC	PS	Moderate	Settled	Remission
16	33	M	8 yr	UC	Total	Moderate	Surgery	—
21	24	F	6 m	CC	Total	Severe	Settled	Remission
23	17	M	10 yr	UC	Total	Severe	Surgery	—
24	39	M	8 yr	UC	Total	Severe	Settled	1 mild attack at 6 months
27	25	M	8 yr	UC	Total	Severe	Settled	Surgery at 3 months after discharge
29	32	M	12 yr	UC	PS	Moderate	Settled	Remission
31	41	M	17 yr	UC	PS	Moderate	Settled	Remission
33	44	F	2 yr	UC	Subtotal	Moderate	Settled	Remission
34	27	F	2 yr	UC	PS	Moderate	Settled	Severe attack at 4 months – surgery
37	60	M	4 yr	CC	Total	Severe	Settled	1 moderate attack at 4 months
40	39	F	8 yr	UC	Total	Moderate	Settled	Remission

UC = ulcerative colitis. CC = Crohn's colitis. SB = small bowel. PS = proctosigmoiditis.

the patients with ulcerative colitis (by far the largest patient subgroup) are considered separately, then two of 18 in the vancomycin group compared with seven of 15 in the control group came to surgery which is a trend (two-tailed Fisher's exact test, p=0·057) in favour of active vancomycin. All the patients in the trial were followed up after its completion for a minimum of one year (Table 2). Three in the vancomycin group and two in the control group have since come to colectomy. No complications attributable to the vancomycin or placebo were encountered in any of the patients studied.

BACTERIOLOGICAL STUDIES

No patient was shown to have a conventional pathogen in their faecal samples. *C difficile* was sought in 38 out of 40 patients and was found in none of them. In the first two patients in the trial, it was not sought for technical reasons. *C difficile* toxin was also sought in patients nos 3–12 and was negative in all instances.

Discussion

There are problems inherent in any therapeutic trial of patients with idiopathic colitis not only because of

Table 3 *Indications for surgery in each patient*

Patient no	*Operation*	*Day of Operation*	*Reason for Operation*
Vancomycin group			
17	Subtotal colectomy*	44	Severe continuous symptoms
30	Subtotal colectomy*	12	Toxic dilatation of the colon
35	Proctocolectomy	7	Severe worsening symptoms
36	Proctocolectomy and ileal resection	30	Severe continuous symptoms
Placebo group			
3	Proctocolectomy	42	Severe continuous symptoms
4	Subtotal colectomy*	21	Toxic dilatation of the colon
6	Proctocolectomy	12	Severe continuous symptoms
10	Subtotal colectomy*	20	Severe continuous symptoms
14	Subtotal colectomy*	4	Toxic dilatation
16	Subtotal colectomy*	46	Severe continuous symptoms
23	Subtotal colectomy*	38	Severe worsening symptoms

* Including preservation of the rectum and mucous fistula.

its unpredictability, but also because there may be a marked variation in the duration, extent and severity of the disease, all of which may affect the response to therapy.[11 15 16] Thus the heterogeneity of our study population may present problems in interpretation of results, particularly in view of the small number of subjects involved. Likewise, a bias might result from the preponderance of patients with recent onset of disease (four out of five) falling by chance into the vancomycin group. Within these limitations, our results suggest that oral vancomycin may reduce the need for operative intervention in patients in exacerbation of ulcerative colitis. In view of the small number of patients with Crohn's disease, it is difficult to make any statement concerning the impact of vancomyin in this group.

There have been no previous controlled trials of antimicrobials in exacerbation of idiopathic colitis, except for those involving sulphasalazine[2 3] nor have there been any previous studies involving vancomycin except in patients with idiopathic colitis complicated by infection with *C difficile* enterotoxin.[7] The reasons for the apparent benefit of vancomycin in patients with ulcerative colitis are unclear. Faecal culture for *C difficile* was negative in the 38 patients in whom it was sought and, in addition, assay for its associated enterotoxin was negative in nine. Ideally, all 40 patients admitted to the study should have had faecal samples analysed for the presence of both *C difficile* and *C difficile* toxin. Nevertheless, these negative results are of interest as they suggest that the efficacy of vancomycin may relate to factor(s) other than faecal carriage of this pathogen, such as the known antimicrobial action of vancomycin on the Gram-positive component of the faecal flora which is profuse in ulcerative colitis.[17–19] To elucidate fully the mode(s) of action of vancomycin in ulcerative colitis would have required detailed microbiological analysis of faecal samples taken before and at intervals after therapy and this was beyond the technical scope of the present study. Indeed, it has been estimated that complete bacteriological characterisation of a single faecal sample may take up to one year to complete.[20]

It could be argued that the dose of vancomycin used was very large particularly in view of the cost of the drug[8 21] (vancomycin 500 mg six hourly × 7 seven days, current NHS price = £315). This criticism probably cannot be justified if vancomycin results in a reduction of the operation rate in colitis and it may be possible to administer the drug in a reduced dosage without losing its apparent benefit.

The negative results for *C difficile* are of interest. Reports from Boston[7 22] and Bristol[23] have demonstrated faecal *C difficile* enterotoxin in as many as 60% of severe exacerbations of idiopathic colitis. These findings are not, however, universal as, apart from the results of this study, Meyers *et al*[24] found *C difficile* enterotoxin in only four out of 44 patients with idiopathic colitis and related its presence not to disease activity but to the antimicrobial drugs these patients had taken previously. These differences in identification rate are unlikely to be due to method because both culture of *C difficile* and the identification of its enterotoxin are now routine. Another explanation for the discrepancy might be prior antimicrobial treatment, but here the data are incomplete[8] and it would be insufficient on its own to explain the degree of difference observed.

Alternatively, different identification rates may relate to epidemiological factors. There is little doubt that outbreaks of *C difficile* occur in hospitals and this might account for the apparent rarity of the organism in one hospital compared with another.[8 25–27] This seems the most likely explanation to account for the negative cultures obtained in this study and the surprisingly high identification rates described by Trnka and LaMont.[7]

Though additional prospective studies on larger numbers of patients are necessary to prove the efficacy of oral vancomycin in ulcerative colitis, the results of this trial show a possible role for this antimicrobial agent in the treatment of exacerbations of the disease. The observed efficacy of

vancomycin was not attributable to its known action against *C difficile,* but suggests a role for the faecal flora in the pathogenesis of ulcerative colitis.

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References

1 Truelove SC, Reynell PC. *Diseases of the digestive tract.* 2nd ed. Oxford: Blackwell Scientific Publications, 1972.

2 Truelove SC, Watkinson G, Draper G. Comparison of corticosteroid and sulphasalazine therapy in ulcerative colitis. *Br Med J* 1962; **2:** 1708–11.

3 Dick AP, Grayson MJ, Carpenter RG, Petrie A. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. *Gut* 1964; **5:** 437–42.

4 Garrod LP, Lambert HP, O'Grady F. *Antibiotic and chemotherapy.* 5th ed. Edinburgh: Churchill Livingstone, 1981: 234–6.

5 Khan MY, Hall WH. Staphylococcal enterocolitis – treatment with oral vancomycin. *Ann Intern Med* 1966; **65:** 1–8.

6 Keighley MRB, Burdon DW, Arabi Y *et al.* Randomised controlled trial of vancomycin for pseudomembranous colitis and postoperative diarrhoea. *Br Med J* 1978; **2:** 1667–9.

7 Trnka YM, LaMont JT. Association of *Clostridium difficile* toxin with symptomatic relapse in chronic inflammatory bowel disease. *Gastroenterology* 1981; **80:** 693–6.

8 Bartlett JG. *Clostridium difficile* and inflammatory bowel disease. *Gastroenterology* 1981; **80:** 863–5.

9 Lennard-Jones JE, Lockhart-Mummery HE, Morson BC. Clinical and pathological differentiation of Crohn's disease and protocolitis. *Gastroenterology* 1968; **54:** 1162–70.

10 Marshak RH, Lundner MD. Radiologic diagnosis of chronic ulcerative colitis and Crohn's disease of the colon. In: Kirsner JB, Shorter RG, eds. *Inflammatory bowel disease.* Philadelphia: Lea and Febiger, 1975: 241–76.

11 Truelove SC, Witts LJ. Cortisone in ulcerative colitis. Final report on a therapeutic trial. *Br Med J* 1955; **2:** 1041–8.

12 Dickinson RJ, Dixon MF, Axon ATR. Staphylococcal enterocolitis and inflammatory bowel disease. *J Clin Pathol* 1980; **33:** 604–5.

13 Hafiz S, Oakley CL. *Clostridium difficile*: isolation and characteristics. *J Med Microbiol* 1976; **9:** 129–37.

14 George RH. A micro-method for detecting toxins in pseudomembranous colitis. *J Clin Pathol* 1979; **32:** 303–4.

15 Driscoll RH, Rosenberg IH. Total parenteral nutrition in inflammatory bowel disease. *Med Clin North Am* 1978; **62:** 185–201.

16 Truelove SC, Willoughby CP, Lee EG, Kettlewell MGW. Further experience in the treatment of severe attacks of ulcerative colitis. *Lancet* 1978; **2:** 1086–8.

17 Seneca H, Henderson E. Normal intestinal bacteria in ulcerative colitis. *Gastroenterology* 1950; **15:** 34–9.

18 Cooke EM. A quantitative comparison of the faecal flora of patients with ulcerative colitis and that of normal persons. *J Path Bacterol* 1967; **94:** 439–44.

19 van der Wiel-Korstanje JA, Winkler KC. The faecal flora in ulcerative colitis. *J Med Microbiol* 1975; **8:** 491–501.

20 Simon GL, Gorbach SL. Intestinal flora in health and disease. *Gastroenterology* 1984; **86:** 174–93.

21 Teasley DG, Gerding DN, Olson M *et al.* Prospective randomised trial of metronidazole versus vancomycin for *Clostridium difficile* – associated diarrhoea and colitis. *Lancet* 1983; **2:** 1043–6.

22 LaMont JT, Trnka YM. Therapeutic implications of *Clostridium difficile* toxin during relapse of chronic inflammatory bowel disease. *Lancet* 1980; **1:** 381–3.

23 Bolton RP, Sheriff RJ, Read AE. *Clostridium difficile* associated diarrhoea: a role in inflammatory bowel disease? *Lancet* 1980; **1:** 383–4.

24 Meyers S, Mayer L, Bottone E, Desmond E, Janowitz HD. Occurrence of *Clostridium difficile* toxin during the course of inflammatory bowel disease. *Gastroenterology* 1981; **80:** 697–700.

25 Milligan ME, Rolfe RD, Finegold SM, George WL. Contamination of a hospital environment by *Clostridium difficile. Curr Microbiol* 1979; **3:** 173–5.

26 Keighley MRB. Antibiotic-associated pseudomembranous colitis: pathogenesis and management. *Drugs* 1980; **20:** 49–56.

27 Greenfield C, Burroughs A, Szawathowski M, Bass N, Noone P, Pounder RE. Is pseudomembraneous colitis infectious? *Lancet* 1981; **1:** 371–2.